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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003904719 for a patent by DBL AUSTRALIA PTY LTD as filed on 01 September 2003.



WITNESS my hand this
Ninth day of September 2004

J. Billingsley

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Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY
ACTIVE AGENTS

Applicant: DBL AUSTRALIA PTY LTD

The invention is described in the following statement:

COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

Field of the Invention

5 The present invention relates to the field of delivery of biologically active agents to a biological system. This field may encompass the delivery of pharmaceutically active agents to a human or animal, or alternatively, it may include the delivery of agricultural or other biologically active chemicals to an insect, plant, soil substrate, body of water or the like.

10

Background of the Invention

15 Biologically active agents ('active agents') such as drugs or agricultural chemicals are typically administered to a biological system such as a human, animal or plant in order to provide a beneficial effect or to prevent a detrimental effect to the system. In many instances it is desirable to sustain the release of the active agent so that the frequency of administration can be reduced. However, controlling the timing, location and duration of release of an active agent in a biological system can be complicated by a number of factors including biological, chemical, and physical barriers within the biological system, as well as the solubility and toxicity of the active agent. Any of these variables may influence the time, duration and location of release of the active agent after administration.

25

Controlling the release of an active agent is also advantageous because the release rate can be predicted and designed to maintain a controlled level of active agent in the biological system for a desired length of time.

30

The design of many controlled release systems is based on the concept of encapsulating the active agent within a polymer so that when the encapsulated active agent is placed into the biological system most of the agent is not

released immediately (so called 'burst release') but rather the release is controlled either by diffusion of the agent through the polymer, or erosion of the polymer to release the active agent.

5 Controlled release polymer encapsulation systems are used in the pharmaceutical field for controlling the release of pharmaceutically active agents in humans and animals. In some cases, these controlled release pharmaceutical preparations are administered orally because this is the most convenient form of administration for the patient. However, many
10 pharmaceutically active agents cannot be administered effectively via the oral route, and have to be administered by injection (parenterally). Some of these polymer based encapsulation delivery systems are subject to hydrolytic reaction, producing acidic products that results in a localised increased acidity which can cause adverse reactions in patients. This disadvantage could be
15 overcome by a delivery system which does not produce such acidic degradation products.

Unfortunately, parenteral administration can require the use of multiple injections or a slow intravenous infusion to attain a desired therapeutic effect.
20 This is particularly the case for active agents that have an undesirable pharmacokinetic profile or where the toxicity of the agent is such that a long infusion is required, or frequent administration of relatively small doses is more preferable than less frequent administration of larger doses. Administration by frequent multiple injections is inconvenient for patients, and labour intensive and
25 costly for the health care provider. For these reasons, there is a need for alternative parenteral delivery systems that have the capacity for delayed or sustained release.

As well as minimising or eliminating problems associated with frequent
30 administration, controlled release is advantageous for active agents that have short half-lives because it is possible to maintain the activity of the agent by sustaining its release into the biological system. Active agents are often

degraded enzymatically or chemically when administered parenterally in the form of a solution or other simple dosage form. One way of preventing or minimising these effects is to administer the agent inside a particle or 'depot' of material that protects the drug from the external environment. In the case of
5 intravenous administration, the size of the particle is important and is usually required to be in the colloidal or sub-micron size.

Additionally, there is a growing need for materials that can act as solubilisers or carriers of an active agent, ie. "excipients", that are non-toxic. The currently
10 approved excipients that are non-toxic are generally not good for the solubilisation of poorly water soluble drugs, so solvents and toxic surfactants such as Cremophor EL are required to produce a therapeutically useful dosage form in solution.

15 From the above discussion it is clear that a new excipient that could provide a combination of one or all of the above features for a parenteral dosage form would be of high value to the pharmaceutical formulation field.

Agricultural chemicals, such as pesticides, fungicides and the like need to be in
20 prolonged contact with the target in order be effective. However, maintaining this contact when the chemical is sprayed on in the form of a solution is highly dependent on the environmental conditions at the time of spraying and thereafter. A presentation of the active agent that is resistant to environmental effects such as rain, and prevents wash off of the chemical from the target is
25 desirable in the agricultural chemical field.

Throughout this specification reference may be made to documents for the purpose of describing the background to the invention or for describing aspects of the invention. However, no admission is made that any reference, including
30 any patent or patent document, cited in this specification constitutes prior art. In particular, it will be understood that, unless otherwise stated, reference to any document herein does not constitute an admission that any of these documents

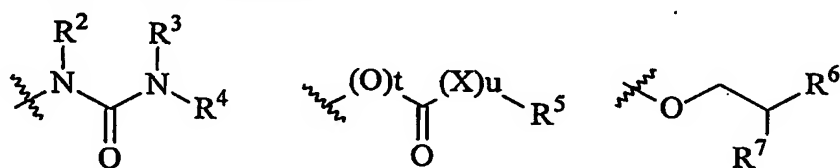
forms part of the common general knowledge in the art in Australia or in any other country. The discussion of the references states what their authors assert, and the applicant reserves the right to challenge the accuracy and pertinency of any of the documents cited herein.

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Summary of the Invention

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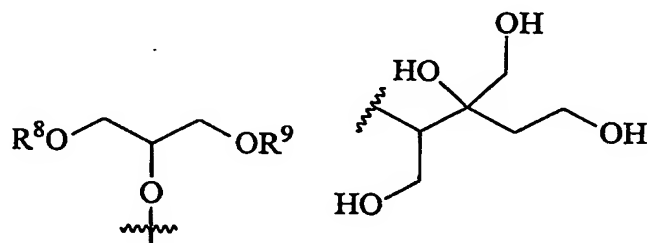
The present invention provides a composition for delivering a biologically active agent to a biological system, the composition including a lyotropic phase containing the biologically active agent, wherein the lyotropic phase is formed from a surfactant that contains a head group selected from the group consisting of any one of structures (I) to (VII):



(I)

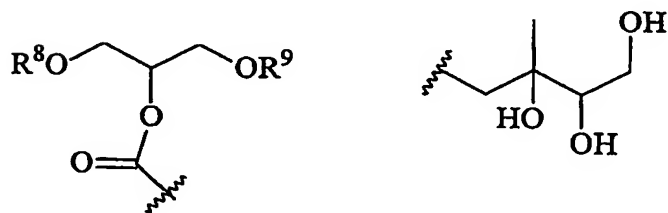
(II)

(III)



(IV)

(V)



(VI)

(VII)

15

in structure (I) R^2 is $-H$, $-CH_2CH_2OH$ or another tail group as defined herein,

in structure (II) X is O, S or N,

t and u are independently 0 or 1.

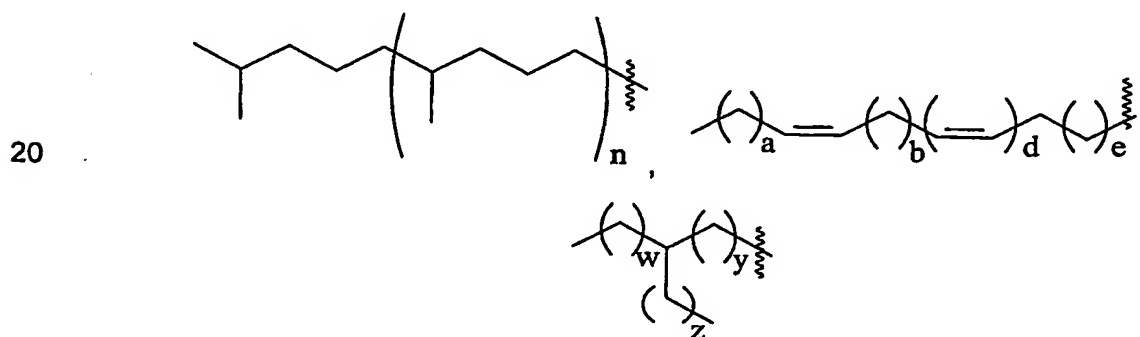
in structure (III) R^6 is $-H$ or $-OH$.

R⁷ is -CH₂OH or -CH₂NHC(O)NH₂, and

15 in structure (IV) and (VI) R^8 is $-H$ or $-alkyl$,

R⁹ is -H or -alkyl.

Preferably, the tail is selected from:



wherein n is an integer from 2 to 6, a is an integer from 1 to 12, b is an integer from 0 to 10, d is an integer from 0 to 3, e is an integer from 1 to 12, w is an integer from 2 to 10, y is an integer from 1 to 10 and z is an integer from 2 to 10.

Preferred surfactant tails are hexahydrofarnesane ((3,7,11-trimethyl)dodecane), phytane ((3,7,11,15-tetramethyl)hexadecane), oleyl (octadec-9-enyl) or linoleyl (octadec-9,12-dienyl) chains.

- 5 Lyotropic phases are phases that are formed by the surfactants in the presence of a solvent. Lyotropic phases generally have distinct topologies depending on the concentration of the surfactant, and this will be discussed in more detail later.
- 10 According to the present invention, the composition may be incorporated into an injectable dosage form. The dosage form may also contain other additives or excipients that are known to those skilled in the relevant art.

15 The present invention also provides a method for delivering a biologically active agent to a biological system, the method including the steps of including the biologically active agent in a lyotropic phase that is formed from the surfactants described in this specification, and administering the lyotropic phase and included agent to the biological system. Alternatively a precursor solution could be used that forms the lyotropic phase on administration by the various routes

20 of parenteral administration, such as intravenous, intramuscular, subcutaneous, topical, transdermal, nasal, buccal, intraocular, vaginal, rectal, intraauricular, periodontal, subdural and epidural.

25 The present invention also provides a method for treating a biological system with a biologically active agent, the method including the step of introducing a composition of the present invention into the biological system so that at least some of the biologically active agent is released to have an effect on the biological system. The method may provide one or more of the following effects: controlled release of the active agent, protection of the active agent

30 from enzymatic or chemical degradation, protection of the active agent from dissolution or slowing of the dissolution process, localisation and maintenance of locality of the active agent in reference to the target biological entity, a less

toxic alternative to known formulations, benefits in processing, handling and/or administration compared to current therapies. For the purpose of this document, toxic is meant in its general sense, but includes adverse reaction to the excipients, drugs, or materials, such as immunological response, allergic response, genotoxicity, carcinogenicity, nephrotoxicity, anaphylaxis, and cytotoxicity.

The present invention also provides a method of forming a sustained release deposit *in situ*, the method including the step of introducing a bolus or precursor solution of the composition of the present invention into the biological system.

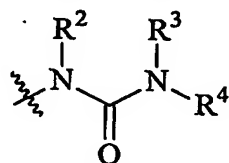
The present invention also provides a delivery system that provides for multiphase release of the active agent. For example, the composition may contain a domain that is extraneous to the lyotropic phase. The extraneous domain may contain the active agent and the kinetics of the release of active agent from the extraneous domain may be different to the release of the active from the lyotropic phase. The active agent may be contained in or may form the extraneous domain. In the extraneous domain all or some of the active agent may be in the form of a solid crystalline particle, an amorphous particle, and/or a solution in a solid or liquid that is immiscible with the surfactants described herein. Alternatively, or in addition the active agent may be encapsulated in a polymeric particle.

For active agents that are not stable in solution form, the present invention provides an alternative formulation strategy to the traditional approaches of freeze-drying, lyophilisation or spray-drying, as the biologically active agent may be protected from the deleterious effects on storage due its incorporation into the composition of the present invention. This provides for greater storage stability, and in the case of a pharmaceutical, easier handling by the health care provider as the reconstitution step can be avoided for this delivery system.

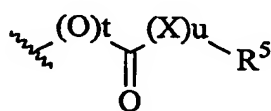
General Description of the Invention

The surfactants that are used in compositions of the present invention are amphiphilic compounds in which the head group forms a charged or uncharged hydrophilic polar region and the tail forms a hydrophobic non-polar region.

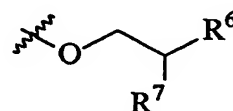
The surfactants of the present invention contain a head group selected from the group consisting of any one of structures (I) to (VII):



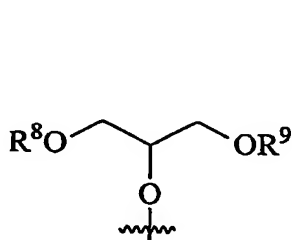
(I)



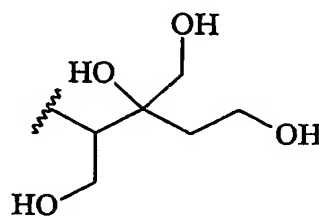
(II)



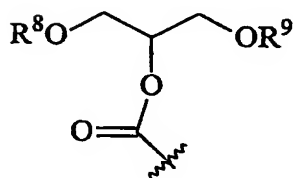
(III)



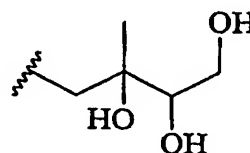
(IV)



(V)



(VI)



(VII)

and a tail selected from the group consisting of a branched alkyl chain, a branched alkyloxy chain or an alkenyl chain, and wherein

in structure (I) R^2 is $-H$, $-CH_2CH_2OH$, or another tail group,
 R^3 and R^4 are independently selected from one or more of
 $-H$, $-C(O)NH_2$, $-CH_2CH_2OH$, or $-CH_2CH(OH)CH_2OH$,

in structure (II) X is O , S or N ,

5

t and u are independently 0 or 1,

R^5 is $-C(CH_2OH)_2alkyl$, $-CH(OH)CH_2OH$,

$-CH_2CH(OH)CH_2OH$ (provided the tail group is not oleyl),

$-CH_2COOH$, $-C(OH)_2CH_2OH$, $-CH(CH_2OH)_2$,

$-CH_2(CHOH)_2CH_2OH$, or

10

$-CH_2C(O)NHC(O)NH_2$,

in structure (III) R^6 is $-H$ or $-OH$,

R^7 is $-CH_2OH$ or $-CH_2NHC(O)NH_2$,

in structures (IV) & (VI) R^8 is $-H$ or $-alkyl$,

R^9 is $-H$ or $-alkyl$.

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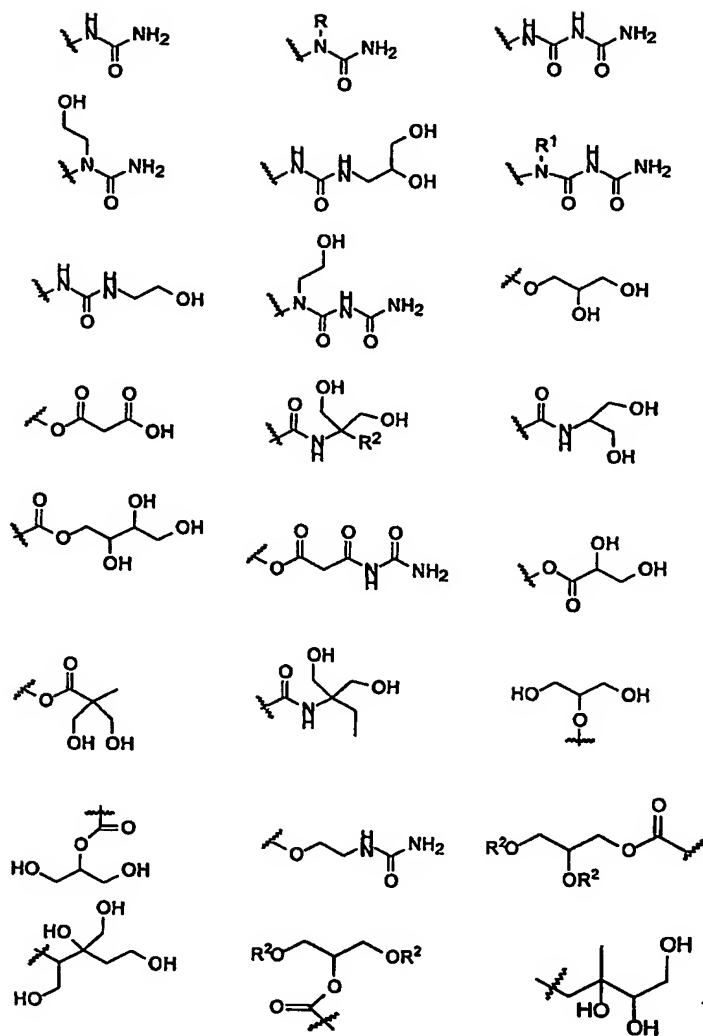
Preferred surfactant tails are hexahydrofarnesane ((3,7,11-trimethyl)dodecane),
phytane ((3,7,11,15-tetramethyl)hexadecane), oleyl (octadec-9-enyl) or linoleyl
(octadec-9,12-dienyl) chains.

20 Preferred surfactant head groups are shown in Table 1.

Combinations of the preferred tails and head groups have either been
synthesised and demonstrated to specifically form or are expected to form
stable lyotropic phases in excess water based on data obtained from the
25 surfactants that have been synthesised to date.

30

Table 1



5 In an aqueous surfactant mixture, water is associated with the head groups of the surfactant which leads to the formation of fluid hydrophilic domains in the mixture. The hydrophobic tails of the surfactant are also screened from the water by the hydrophilic head groups to thereby form a hydrophobic domain. The fluidity of the hydrophilic domain allows the native geometry of the surfactant molecule to determine the orientation, and spatial aspects of arrangement of the surfactant molecules at the interface between the hydrophilic and hydrophobic domains. This arrangement is often called the 'curvature', because the interface can be curved towards the hydrophilic or hydrophobic domains. The hydrophilic and hydrophobic domains are

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sometimes referred to as the water and oil domains, respectively. The addition of greater amounts of water to the surfactant alters the average curvature of the interface, potentially resulting in a variety of particular topologies that can be displayed by a surfactant-solvent system at equilibrium. At equilibrium, these topologies are often termed 'mesophases', 'lyotropic phases', 'liquid crystalline phases', or just 'phases'.

If the average curvature of the interface in a surfactant-solvent system is towards the hydrophobic or oil domain, then the mesophases are usually identified as being 'water-continuous' and of the 'normal' type. If the curvature is towards the hydrophilic or water domain, they are termed 'oil-continuous' and are said to be of the 'reverse' or 'inverse' type. If the average curvature is balanced between the two, the system has an average net curvature close to zero, and the resulting phases may be of a stacked lamellar-type structure, or a structure often termed 'bicontinuous', consisting of two intertwined, non-intersecting, hydrophilic and hydrophobic domains. Other topologies, generally termed 'intermediate phases' may also exist, such as the ribbon, mesh and non-cubic bicontinuous phases.

Examples of the particular topologies that can be formed in surfactant-solvent systems include micellar (normal or reverse), hexagonal (normal or reverse), lamellar, and cubic (normal, reverse or bicontinuous), among others.

Micellar phase includes micelles which form when surfactant molecules self-assemble to form aggregates due to the head groups associating with water, and the tails associating with other tails to form a hydrophobic environment. Normal micelles consist of a core of hydrophobic tails surrounded by a shell of head groups extending out into water. Addition of a poorly water-soluble oil will result in some oil being incorporated (or solubilized) into the hydrophobic interior core of the micelles, until a limit in the capacity is reached. Addition of further oil results in the formation of a separate oil phase excluded from the micellar solution, and the system is said to be phase separated.

Reverse micelles are directly analogous to the normal micelles except that the core of the micelles contain water in association with the head groups and the tails extend into a hydrophobic domain. Addition of an oil dilutes the micelles as discrete entities, and addition of water 'swells' the reverse micelles until the capacity of the core to solubilize water is exceeded, resulting in phase separation.

Normal and reverse micelles may be spherical, rod-like or disk shaped, depending on the molecular geometry of the surfactant, but at low enough concentration the system is essentially isotropic.

Normal hexagonal phase occurs when the system consists of long, rod-like micelles at very high concentration in water, packed into a hexagonal array. As such the system possesses order in two dimensions. This imparts an increased viscosity on the system, and the anisotropy allows visualisation of the birefringent texture when viewed on a microscope through crossed polarising filters. Again, reverse hexagonal phase is the oil continuous version of the normal hexagonal phase, with water-core micelles in a close packed hexagonal array.

Lamellar phase consists of a stacked bilayer arrangement, where opposing monolayers of headgroups are separated by the water domain to form a hydrophilic layer, while the tails of the back to back layers are in intimate contact to form a hydrophobic layer. Lamellar phase is favoured when the structure of the surfactant is such that the head groups and the tails occupy substantially equivalent volumes in solution.

Cubic phase consists of two main types, bicontinuous and micellar. Normal and reverse cubic phases of the micellar type consist of close packed spherical micelles in a cubic array, where either the water and headgroups, or the tails form the interior of the micelles. They are generally of high viscosity, but

because they consist of spherical micelles these systems are isotropic, so no birefringent texture is observed.

Bicontinuous cubic phases form when the molecular geometry of a surfactant molecule is well balanced, such that the net curvature is zero. This results in a so-called 'infinite periodic lattice structure', in which the hydrophobic and hydrophilic domains are intertwined but do not intersect. The bicontinuous cubic phases, while consisting of bilayers, have long range order based on a cubic unit cell, and hence are also seen to be isotropic when viewed through crossed polarised light. For the purposes of the present invention, bicontinuous phases may be considered 'lyotropic phases', 'reverse lyotropic phases' or 'reverse liquid crystalline phases'.

Preferably, the composition of the present invention contains a lyotropic phase that is selected from the group consisting of a reverse micellar phase, a bicontinuous cubic phase, a reverse intermediate phase and a reverse hexagonal phase. Most preferably the reverse lyotropic phase that is formed is a bicontinuous cubic phase or a reversed hexagonal phase.

Using some of the surfactants described herein it has been found that lyotropic phases can be formed at 40°C or less and that they are stable at these temperatures and in the presence of excess water.

As used herein the term 'controlled release' means that release of the active agent from the composition is either delayed or sustained and the timing and or location of release of the active agent in the biological system is different to that of the active agent alone or in solution, or in another dosage form. It will be appreciated that in the compositions of the present invention the active agent is not necessarily covalently bound to the surfactant. Rather, the active agent may be dissolved, complexed or in a complex form, or in a salt form, and is included within the lyotropic phase and it may reside in the hydrophobic domain, the hydrophilic domain, or in the interfacial region of the lyotropic phase.

Alternatively, the active agent may be distributed between the various domains by design or as a result of the natural partitioning processes. If the active agent is amphiphilic it may reside in one or any number of these domains simultaneously.

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Without intending to be bound by theory, it is thought that for a period of time after administration of the composition of the present invention, the active agent will be released primarily through diffusion of the active agent out of the lyotropic phase by concentration gradient and/or partitioning processes.

10 However, the composition or lyotropic phase may also be subject to degradation over time by enzymatic or chemical attack, and this may provide a further mechanism for release of the active agent. When the composition is in the form of colloidal particles, the particles may also be subject to other biological processes such as removal from the bloodstream by the reticulo-
15 endothelial system. These processes may further alter release of the active agent, and may act as a depot or reservoir for the active agent, and may aid in targetting the release of pharmaceutical drugs to specific organs such as the liver and kidneys. In addition, the composition may be subjected to mechanical breakdown or exposure to temperature or other environmental effects.

20

The thermodynamic stability of the lyotropic phases to dilution in excess aqueous solution means that they can be dispersed to form particles of the lyotropic phase. Particles containing cubic phase or hexagonal phase are sometimes referred to as cubosomes or hexosomes, respectively. For many
25 applications it is advantageous for the composition of the present invention to be a colloidal solution or suspension of the lyotropic phase containing the biologically active agent, suspended in a suitable liquid carrier. Most preferably the liquid carrier is water. Alternatively the composition may be a freeze-dried, lyophilised or spray-dried powder comprised in part of particles loaded with
30 active agent.

The 'active agent' or 'biologically active agent' that is used in compositions of the present invention may be any substance that is intended for use in the diagnosis, cure, mitigation, treatment or prevention of an undesirable state in the biological system. For example, the active agent may be a drug that is used therapeutically to treat or prevent a disease state in humans or animals. Alternatively, the active agent may be an agrochemical that is used to treat or prevent a disease state in plants. Alternatively, the active agent may be a pesticide, insecticide or algicide that is used to treat an area of land or a body of water. Examples of active agents include pharmaceutical actives, therapeutic actives, cosmetic actives, veterinarial actives, nutraceuticals, growth regulators, pesticides, insecticides, algicides, fungicides, herbicides, weedicides, sterilants, pheromones, nematocides, repellents, nutrients, fertilisers, proteinaceous materials, genes, chromosomes, DNA and other biological materials.

15

The composition of the present invention may be particularly suitable for the delivery of insoluble or poorly soluble active agents, and in particular poorly soluble pharmaceutically active agents for human and veterinary medicine.

20 Examples of some poorly soluble pharmaceutically active agents that could be included in compositions of the present invention include immunosuppressive agents such as cyclosporins including cyclosporine (cyclosporin A), immunoactive agents, antiviral and antifungal agents, antineoplastic agents, analgesic and anti-inflammatory agents, antibiotics, anti-epileptics, anesthetics, 25 hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, anticonvulsant agents, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergic and antiarrhythmics, antihypertensive agents, hormones, and nutrients. A detailed description of these and other suitable agents may be 30 found in Remington's Pharmaceutical Sciences, 18th edition, 1990, Mack Publishing Co. Philadelphia, Pa.

Importantly, the present invention allows for the incorporation of agents of very different physico-chemical properties into a single dosage form. Because the composition of the invention comprises hydrophilic, hydrophobic, and interfacial domains, the incorporation of hydrophilic, lipophilic, hydrophobic and amphiphilic compounds in any combination is possible, and the release of all of these materials may be controlled. This provides a particular advantage over other forms of delivery systems, such as emulsions, liposomes, and polymeric encapsulation systems. Whilst compositions of the present invention may be particularly suitable for the delivery of poorly water-soluble pharmaceutically active agents, the invention is not restricted to that application and the active agent may be any pharmaceutically active agent that requires administration to a human or animal. The pharmaceutically active agent may be any substance that is used to prevent or treat a disease state, including any pharmaceutically active synthetic or naturally occurring organic or inorganic molecules, proteins, peptides, vaccines, and components thereof.

The composition of the present invention may be particularly suitable for the controlled release delivery of agents that cannot otherwise be effectively administered by the oral route to human patients because of poor or inconsistent systemic absorption from the gastrointestinal tract, or poor stability in the gastrointestinal environment. These agents are currently administered via intravenous routes, requiring frequent intervention by a physician or other health care professional, entailing considerable discomfort and potential local trauma to the patient and even requiring administration in a hospital setting. In contrast, parenteral administration of such active agents in compositions of the present invention may lead to a controlled release of the active agent which may mean that the agents have to be administered less frequently.

An example of an active agent that currently requires administration by intravenous infusion is paclitaxel. Paclitaxel is currently marketed as TAXOL™ and it is one of the important classes of cytotoxic agents which are not normally bioavailable when administered orally to humans. In addition to poor oral

bioavailability, the toxicity of paclitaxel means that it has to be administered over an extended period of time in order to reduce the toxic effects of the dosage. Accordingly, paclitaxel (and many other chemotherapeutic drugs) is typically administered by continuous intravenous infusion, which may take several hours.

5 Compositions of the present invention provide alternative administration regimes, in which release of an active agent from the colloidally dispersed particles of the invention, administered by injection can be sustained *in vivo*. As a consequence of the sustained release the active agent may not have to be administered as frequently.

10

Compositions of the present invention also provide injectable pharmaceutical formulations of active agents that are currently available only as injectable formulations by virtue of them containing organic solvents, surfactants or other toxic excipients. The example given above of paclitaxel is one such active agent.

15

Intravenous administration would most likely be in the form of administration of a colloidal dispersion of the lyotropic phase of the invention containing the active agent. The colloidal particle would be free to circulate throughout the blood compartment and may or may not be taken into other tissues. Slow controlled release of drug from the particles would provide drug in a similar manner as a slow infusion, but be achieved by a single or multiple injection of the colloidal dispersion. Alternatively, the colloidal dispersion may be formed *in vivo*, by administration of a precursor solution that forms the colloidal particles on contact with body fluids. Alternatively, a bolus injection of bulk reverse lyotropic phase containing the active agent, or a precursor solution containing the active agent which forms the bulk lyotropic phase on contact with body fluids, may be used to form a depot of the composition in the body. Release of the active agent from the depot therefore provides for release of the agent in a similar manner to the usual infusion method except by way of an injectable depot. The invention provides an alternative depot type to the currently available systems, such as microspheres, hydrogels and the like. The colloidal

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and bolus injection form of the invention may also contain an active agent in a form other than dissolved in the invention itself, such as a solid crystalline particle, an amorphous particle, a solution in a solid or liquid that is immiscible in the present invention, encapsulated in a polymeric particle, or otherwise
5 contained in or form an extraneous domain to that of the invention. This form of the invention (in the case of a bolus injection in particular) may provide for very slow, possibly multiphase release of the active agent, which may provide benefits by increasing the depot lifetime. Degradation of the materials comprising the depot form of the present invention is also envisaged to be less
10 toxic to local tissues than that of conventional polymeric materials used in these dosage forms, due to the lesser effect on local acidity.

Administration routes which lead to systemic or localised treatment of disease, parasitic and bacterial infestations and the like would include, without
15 limitations: intravenous, subcutaneous, intramuscular, intraperitoneal, subdural, epidural, intrapulmonary, topical, transdermal, nasal, buccal, intraocular, vaginal, rectal, intraauricular, periodontal.

Compositions of the present invention can potentially be used to localise a
20 pharmaceutically active agent in certain tissue types, such as tumours and the tissues of the reticulo-endothelial system. The depot form of the invention would be most suited to this purpose providing a reservoir of drug to locally treat the condition of the tissue.

25 Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or
30 vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils

(such as soybean oil, mono-, di- and triglycerides, fatty acids, α -tocopherol and the like), and injectable organic esters such as ethyl oleate.

5 These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, or dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, EDTA and the like. Cryoprotectants, spray drying adjuvants, such as starches and dextrans, buffers, isotonicity adjusting agents, and pH adjusting materials
10 may also be contained in the compositions of the invention.

The compositions may also be subjected to further treatment processes to render them suitable for use in a particular application. For example, compositions may be sterilised by means of an autoclave, sterile filtration,
15 radiation techniques or by incorporating sterilising agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use. The compositions can also be processed by various means, such as homogenisation, sonication and extrusion, so as to achieve a satisfactory particle size distribution and surface
20 properties.

Colloidal particles or compositions containing them may be further stabilised using a stabilising agent. A variety of agents suitable for this purpose are commonly used in other colloidal systems and may be suitable for the present
25 purposes. For example, poloxamers, phospholipids, alginates, amylopectin and dextran may be used to enhance stability. Addition of a stabilising agent preferably does not affect the final structure or the physical properties of the particles or compositions.

30 Compositions of the present invention may also be modified by the addition of additives, such as glycerol, sucrose, phosphate buffers, dextrose, sorbitol and

saline in appropriate concentrations, to the aqueous medium without changing the principal structure of the particles.

5 Formulations containing the composition of the present invention may conveniently be presented in unit-dose or multi-dose containers, e.g. sealed ampoules and vials.

10 It is contemplated that the attending clinician will determine, in his or her judgement, an appropriate dosage and regimen, based on the patient's age and condition as well as the severity of the condition that is being treated.

15 As well as use in the pharmaceutical field, the composition of the present invention may also be used for the delivery of agricultural chemicals. In use, many agricultural chemicals are broken down or degraded in the environment into which they are released and for this reason there is a need to re-apply the chemicals in order to maintain an effective level of chemical in the substrate. The environmental conditions also make it difficult to maintain consistent contact between the target and the chemical. For example, agricultural chemicals in liquid form are often administered to crops by spraying. Using the
20 composition of the present invention a crop may be sprayed with a lower dose of agricultural chemicals, due to increased efficiency of delivery of chemical to the target. Additionally, in some forms of the invention the release of the agricultural chemicals will be sustained and therefore will need to be administered less frequently.

25

In the case that the target biological entity is a plant, the active agent delivered using the compositions of the invention would potentially include but not be limited to synthetic pyrethroids such as alpha-cypermethrin, benzyl ureas such as diflubenfuron, organophosphorous compounds for example mevinphos,
30 triazines such as cyanazine, and plant hormone regulators such as MCPA.

Description of the Figures

Aspects of preferred embodiments of the invention are shown in the accompanying figures. However, it is to be appreciated that the figures and the
5 following description is not to limit the generality of the invention.

Figure 1 is a time vs % released plot for the release of Paclitaxel from 2,3-dihydroxypropionic acid octadec-9-enyl ester + water reverse hexagonal phase delivery system.

10

Figure 2 is a time vs % released plot for the release of Irinotecan hydrochloride from 2,3-dihydroxypropionic acid octadec-9-enyl ester + water reverse hexagonal phase delivery system.

15 Figure 3 is a time vs % released plot for the release of Irinotecan base from 2,3-Dihydroxypropionic acid octadec-9-enyl ester + water reverse hexagonal phase delivery system.

Figure 4 is a time vs % released plot for the release of Irinotecan base from 2,3-
20 Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester + water reverse hexagonal phase delivery system.

Figure 5 is a time vs % released plot for the release of octreotide acetate from a 2,3-Dihydroxypropionic acid octadec-9-enyl ester + water delivery system.

25

Figure 6 is a time vs % released plot for the release of octreotide acetate from a 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester + water delivery system.

30 Figure 7 is a time vs % released plot for the release of octreotide acetate from an injectable composition of octreotide acetate, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and water.

Figure 8 is a time vs % released plot for the release of octreotide acetate from an injectable composition of octreotide acetate, 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester and water.

5

Figure 9 is a time vs % released plot for the release of histidine from a 2,3-Dihydroxypropionic acid octadec-9-enyl ester + water delivery system.

10 Figure 10 is a time vs % released plot for the release of histidine from a 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester + water delivery system.

15 Figure 11 is a time vs % released plot for the release of risperidone from an injectable precursor solution of risperidone, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and water.

20 Figure 12 is a time vs % released plot for the release of FITC-dextran from an injectable precursor composition of FITC-dextran, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and water.

25 Description of Preferred Embodiments of the Invention

The invention will now be described with reference to examples that are directed particularly to the area of pharmaceutical drug delivery. However, in light of the foregoing discussion, it will be appreciated that the invention is not
30 limited to that particular field.

Example 1 – Solubility of Biologically Active Agents in Surfactants

5 In order for the surfactants to be useful as components of the delivery system, it is important to be able to dissolve biologically active agents in the surfactant or in the water. Table 1 illustrates that the surfactants are useful for dissolving three pharmaceutical compounds that may potentially be delivered using the invention. Solubility was determined by saturation of the surfactant with solid drug at 40°C until saturation is achieved. Drug level was determined by reverse
10 phase HPLC. Values given are the mean of three separate samples \pm standard deviation, unless denoted otherwise.

Surfactant	Solubility (mg/g)		
	Paclitaxel	Irinotecan HCl	Irinotecan base
2,3-Dihydroxypropionic acid octadec-9-enyl ester	8.43 \pm 0.23	9.69 \pm 0.74	35.66 \pm 1.26
2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester	4.83 \pm 0.83	4.33 \pm 0.37	64.54 \pm 4.65
3,7,11-Trimethyl-dodecyl urea	34.65 \pm 2.34	33.83 \pm 5.98	3.76 \pm 0.45
3,7,11,15-Tetramethyl-hexadecyl urea	7.85 \pm 1.93	1.63 \pm 0.64	0.44 \pm 0.11
1-(3,7,11,15-tetramethyl-hexadecyl)-3-(2-hydroxyethyl) urea	5.67 \pm 1.64	4.36 \pm 0.30	0.94 \pm 0.02
1-(3,7,11,15-tetramethyl-hexadecyl)-1-(2-hydroxyethyl) urea	0.87 \pm 0.18	0.43 \pm 0.20	0.35 \pm 0.001
3,7,11,15-tetramethyl-hexadecanoic acid 1-glycerol ester	6.66 ^a	ND	6.22 ^a
2,3-Dihydroxypropionic acid 3,7,11-trimethyl-dodecyl ester	7.25 ^b	4.58 ^a	3.92 ^b

^a single determination; ^b mean of duplicate determination; ND = not determined

15 Sustaining the release of biologically active agents is an important aspect of the present invention. Release from the bulk lyotropic phase was determined as it provides a model system for the expected behaviour of the system as an

injectable depot. It is also envisaged that the slowing of the release from the bulk phase may give insights into the behaviour of the colloidal dispersion of the same material. A simple method was developed which allows the measurement of drug release from a tablet-sized sample of bulk reverse phase.

5

Example 2 – Sustained release of Paclitaxel from a composition of Paclitaxel, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water

10 Example of the sustained release of paclitaxel from the lyotropic phase formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester is shown in Figure 1. A tablet sized sample of reverse hexagonal phase containing drug was prepared as follows. Paclitaxel was dissolved in 300 mg of neat surfactant at close to the saturated solubility value listed in Table 1. The viscous lyotropic bulk phase was formed in a 2 mL screw top glass vial by adding excess water (700 μ L) to the surfactant solution with vortex mixing. The sample was equilibrated for 3-4
15 days in a 40°C incubator in the presence of excess water and centrifugation was used to form a viscous plug of lyotropic phase. A sample of the viscous phase was removed and placed into a round microbeaker (purpose-built), which is 10mm diameter across its horizontal circular cross section and 10 mm high.
20 This allowed a constant geometry of the sample surface for release to external solution. The microbeaker was attached to a large magnetic stirrer to anchor it to the bottom of the jacketed glass vessel used to hold the release medium. The release medium was 500 mL of deionised water maintained at 40°C and stirring was provided by an overhead stirrer with 30 mm tri-blades rotating at 100 \pm 1
25 rpm. The glass vessel was sealed to avoid evaporation of the release medium. Samples were taken at regular intervals, an identical volume of release medium replaced, and the samples were analysed for paclitaxel content. The release experiment was halted after 10 days, as the sustained release nature of the sample had been demonstrated. It is important to note that there is no
30 membrane present in this experiment, which has complicated the interpretation of previous release determinations in similar systems.

Example 3 – Sustained release of Irinotecan HCl from a composition of Irinotecan Hydrochloride, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water

5 Example of the sustained release of irinotecan hydrochloride from the lyotropic phase formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester is shown in Figure 2. A tablet sized sample of reverse hexagonal phase containing drug was prepared as follows. Irinotecan hydrochloride was dissolved in 300 mg of neat surfactant at close to the saturated solubility value listed in Table 1. The
10 viscous lyotropic bulk phase was formed in a 2 mL screw top amber glass vial by adding excess water (700 μ L) to the surfactant solution with vortex mixing. The sample was equilibrated for 3-4 days in a 40°C incubator in the presence of excess water and centrifugation was used to form a viscous plug of lyotropic phase. A sample of the viscous phase was removed and placed into a round
15 microbeaker (purpose-built), which is 10mm diameter across its horizontal circular cross section and 10 mm high. This allowed a constant geometry of the sample surface for release to external solution. The microbeaker was attached to a large magnetic stirrer to anchor it to the bottom of the jacketed glass vessel used to hold the release medium. The release medium was 500 mL of
20 deionised water maintained at 40°C and stirring was provided by an overhead stirrer with 30 mm tri-blades rotating at 100 \pm 1 rpm. The glass vessel was sealed to avoid evaporation of the release medium, and was covered in foil to protect the drug from degradation induced by light. Samples were taken at regular intervals and stored in amber glass vials, an identical volume of release
25 medium replaced, and the samples were analysed for irinotecan content. The release experiment was halted after 15 days, as the sustained release nature of the sample had been demonstrated. It is important to note that there is no membrane present in this experiment, which has complicated the interpretation of previous release determinations in similar systems.

Example 4 – Sustained release of Irinotecan base from a composition of Irinotecan base, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water

Example of the sustained release of irinotecan base from the lyotropic phase formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester is shown in Figure 3. A tablet sized sample of reverse hexagonal phase containing drug was prepared as follows. Irinotecan base was dissolved in 300 mg of neat surfactant at close to the saturated solubility value listed in Table 1. The viscous lyotropic bulk phase was formed in a 2 mL screw top amber glass vial by adding excess water (700 μ L) to the surfactant solution with vortex mixing. The sample was equilibrated for 3-4 days in a 40°C incubator in the presence of excess water and centrifugation was used to form a viscous plug of lyotropic phase. A sample of the viscous phase was removed and placed into a round microbeaker (purpose-built), which is 10mm diameter across its horizontal circular cross section and 10 mm high. This allowed a constant geometry of the sample surface for release to external solution. The microbeaker was attached to a large magnetic stirrer to anchor it to the bottom of the jacketed glass vessel used to hold the release medium. The release medium was 500 mL of deionised water maintained at 40°C and stirring was provided by an overhead stirrer with 30 mm tri-blades rotating at 100 ± 1 rpm. The glass vessel was sealed to avoid evaporation of the release medium, and was covered in foil to protect the drug from degradation induced by light. Samples were taken at regular intervals and stored in amber glass vials, an identical volume of release medium replaced, and the samples were analysed for irinotecan content. The release experiment was halted after 12 days, as the sustained release nature of the sample had been demonstrated. It is important to note that there is no membrane present in this experiment, which has complicated the interpretation of previous release determinations in similar systems.

Example 5 – Sustained release of Irinotecan base from a composition of Irinotecan base, 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester and Water

- 5 Example of the sustained release of irinotecan base from the lyotropic phase formed by 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester is shown in Figure 4. A tablet sized sample of reverse hexagonal phase containing drug was prepared as follows. Irinotecan base was dissolved in 300 mg of neat surfactant at close to the saturated solubility value listed in Table 1.
- 10 The viscous lyotropic bulk phase was formed in a 2 mL screw top amber glass vial by adding excess water (700 μ L) to the surfactant solution with vortex mixing. The sample was equilibrated for 3-4 days in a 40°C incubator in the presence of excess water and centrifugation was used to form a viscous plug of lyotropic phase. A sample of the viscous phase was removed and placed into a
- 15 round microbeaker (purpose-built), which is 10mm diameter across its horizontal circular cross section and 10 mm high. This allowed a constant geometry of the sample surface for release to external solution. The microbeaker was attached to a large magnetic stirrer to anchor it to the bottom of the jacketed glass vessel used to hold the release medium. The release
- 20 medium was 500 mL of deionised water maintained at 40°C and stirring was provided by an overhead stirrer with 30 mm tri-blades rotating at 100 \pm 1 rpm. The glass vessel was sealed to avoid evaporation of the release medium, and was covered in foil to protect the drug from degradation induced by light.
- 25 Samples were taken at regular intervals and stored in amber glass vials, an identical volume of release medium replaced, and the samples were analysed for irinotecan content. The release experiment was halted after 12 days, as the sustained release nature of the sample had been demonstrated. It is important to note that there is no membrane present in this experiment, which has
- 30 complicated the interpretation of previous release determinations in similar systems.

Example 6 – Formulation of hydrophilic compounds in injectable 2,3-Dihydroxypropionic acid octadec-9-enyl ester

5 In order to be useful for delivery of hydrophilic agents with low solubility in the surfactant, an injectable composition ("Precursor") was developed, in which the hydrophilic drug is dissolved in a polar internal phase, and this is mixed with surfactant in such proportions that a low viscosity lyotropic phase is produced. This precursor contains polar liquid at such a composition that it is below the threshold required to form the highly viscous, non-syringable reverse hexagonal
10 or reverse cubic phase until it is in contact with further polar liquid, such as bodily fluids on injection. One example of such an injectable precursor is described:

15 Octreotide acetate (15.1mg) was dissolved in 105 µL pH4 acetate buffer (BP), and 70 µL of this solution was added to molten 2,3-dihydroxypropionic acid octadec-9-enyl ester at 37°C in a glass vial. After rotating on a tube roller at 37°C for one hour, a transparent homogeneous low viscosity liquid was obtained. Injection of this precursor into water using an 18 gauge hypodermic needle and syringe, when viewed through crossed polarising filters, produced a
20 highly birefringent phase in water virtually on contact with excess water.

Example 7 – Formulation of hydrophilic compounds in injectable Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester

25 One example of such an injectable precursor is described:

Octreotide acetate (25.0 mg) was dissolved in 175 µL pH4 acetate buffer (BP), and 70 µL of this solution was added to dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester at 37°C in a glass vial. After rotating on a tube roller
30 at 37°C for one hour, a transparent homogeneous low viscosity liquid was obtained. Injection of this precursor into water using an 18 gauge hypodermic

needle and syringe, when viewed through crossed polarising filters, produced a highly birefringent phase in water immediately on contact with excess water.

5 Example 8 – Sustained release of octreotide acetate from a composition of Octreotide Acetate, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water

Sustained release of a peptide is often desirable for long term therapy by release of peptide after depot injection. This example demonstrates the release of a representative therapeutic peptide from the reverse phase formed by one of
10 the surfactants of the invention:

Data for the sustained release of octreotide acetate from the lyotropic phase formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester are shown in Figure 5. Octreotide acetate (20mg) was dissolved in 500 µL of pH4 acetate buffer
15 (BP). This solution was added to 750mg 2,3-dihydroxypropionic acid octadec-9-enyl ester in a glass vial, which was rotated on a tube roller at 37°C for 48 hours. The vial was centrifuged and excess aqueous solution removed. A 0.8 g sample of the viscous phase was removed and placed into a small dialysis sac (Spectrapor 1) containing 5 mLs of pH4 acetate buffer, sealed, and placed
20 in a 50 mL polypropylene tube containing a further 45 mLs of pH4 acetate buffer. This was sealed and placed on a shaking water bath at 80 rpm, 37°C. Samples were taken from the external buffer solution at regular intervals, an identical volume of release medium replaced, and the samples were analysed for octreotide content by HPLC.

25

Example 9 – Sustained release of octreotide acetate from a composition of Octreotide Acetate, Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester and Water

30 Sustained release of a peptide is often desirable for long term therapy by release of peptide after depot injection. This example demonstrates the release

of a representative therapeutic peptide from the reverse phase formed by one of the surfactants of the invention:

5 Data for the sustained release of octreotide acetate from the lyotropic phase formed by 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester are shown in Figure 6. Octreotide acetate (20mg) was dissolved in 500 μ L of pH4 acetate buffer (BP). This solution was added to 700 mg 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester in a glass vial, which was rotated on a tube roller at 37°C for 48 hours. The vial was
10 centrifuged and excess aqueous solution removed. A 0.8 g sample of the viscous phase was removed and placed into a small dialysis sac (Spectrapor 1) containing 5 mLs of pH4 acetate buffer, sealed, and placed in a 50 mL polypropylene tube containing a further 45 mLs of pH4 acetate buffer. This was sealed and placed on a shaking water bath at 80 rpm, 37°C. Samples were
15 taken from the external buffer solution at regular intervals, an identical volume of release medium replaced, and the samples were analysed for octreotide content by HPLC.

Example 10 – Sustained release of octreotide acetate from an injectable precursor composition of Octreotide Acetate, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water
20

Sustained release of a peptide is often desirable for long term therapy by release of peptide after depot injection. This example demonstrates the release
25 of a representative therapeutic peptide from the reverse phase formed by one of the surfactants of the invention when formulated as a low viscosity injectable liquid:

Data for the sustained release of octreotide acetate from injectable precursor
30 based on 2,3-dihydroxypropionic acid octadec-9-enyl ester are shown in Figure 7. Octreotide acetate (10mg) was dissolved in 70 μ L of pH4 acetate buffer (BP). This solution was added to 930 mg 2,3-dihydroxypropionic acid octadec-9-enyl

ester in a glass vial, which was rotated on a tube roller at 37°C for 1 hour. The entire sample of low viscosity precursor was injected into a 1 mL air-filled soft gel capsule, and placed into a 50 mL polypropylene tube containing 50mLs of pH4 acetate buffer. This was sealed and placed on a shaking water bath at 80 rpm, 37°C. Samples were taken from the solution at regular intervals, an identical volume of release medium replaced, and the samples were analysed for octreotide content by HPLC.

Example 11 – Sustained release of octreotide acetate from an injectable precursor composition of Octreotide Acetate, Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester and Water

Sustained release of a peptide is often desirable for long term therapy by release of peptide after depot injection. This example demonstrates the release of a representative therapeutic peptide from the reverse phase formed by one of the surfactants of the invention when formulated as a low viscosity injectable liquid:

Data for the sustained release of octreotide acetate from injectable precursor based on 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester are shown in Figure 8. Octreotide acetate (10mg) was dissolved in 70 µL of pH4 acetate buffer (BP). This solution was added to 930 mg 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester in a glass vial, which was rotated on a tube roller at 37°C for 1 hour. The entire sample of low viscosity precursor was injected into a 1 ml air-filled soft gel capsule, and placed into a 50 mL polypropylene tube containing 50mLs of pH4 acetate buffer. This was sealed and placed on a shaking water bath at 80 rpm, 37°C. Samples were taken from the solution at regular intervals, an identical volume of release medium replaced, and the samples were analysed for octreotide content by HPLC.

Example 12 – Sustained release of histidine from a composition of histidine, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water

Sustained release of a small hydrophilic compound is often desirable for long term therapy by release of peptide after depot injection. This example demonstrates the release of a representative small hydrophilic molecule, histidine, from the reverse phase formed by one of the surfactants of the invention:

- 10 Data for the sustained release of histidine from the lyotropic phase formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester are shown in Figure 9. Histidine (10mg) was dissolved in 1 mL of pH4 acetate buffer (BP). This solution was added to 1078 mg 2,3-dihydroxypropionic acid octadec-9-enyl ester in a glass vial, which was rotated on a tube roller at 37°C for 48 hours.
- 15 The vial was centrifuged and excess aqueous solution removed. A 1g sample of the viscous phase was removed and placed into a small dialysis sac (Spectrapor 1) containing 5 mLs of pH4 acetate buffer, sealed, and placed in a 50 mL polypropylene tube containing a further 45 mLs of pH4 acetate buffer. This was sealed and placed on a shaking water bath at 80 rpm, 37°C. Samples
- 20 were taken from the external buffer solution at regular intervals, an identical volume of release medium replaced, and the samples were analysed for histidine content by HPLC.

Example 13 – Sustained release of histidine from a composition of histidine, Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester and Water

- 25 Data for the sustained release of histidine from the lyotropic phase formed by 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester are shown in Figure 10. Histidine (10mg) was dissolved in 1 mL of pH4 acetate buffer (BP). This solution was added to 1078 mg 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester in a glass vial, which was rotated on a tube roller at 37°C for 48 hours. The vial was centrifuged and excess aqueous solution
- 30

removed. A 1g sample of the viscous phase was removed and placed into a small dialysis sac (Spectrapor 1) containing 5 mLs of pH4 acetate buffer, sealed and placed in a 50 mL polypropylene tube containing a further 45 mLs of pH4 acetate buffer. This was sealed and placed on a shaking water bath at 80 rpm, 37°C. Samples were taken from the external buffer solution at regular intervals, an identical volume of release medium replaced, and the samples were analysed for histidine by HPLC.

Example 14 – Sustained release of risperidone from an injectable precursor composition of risperidone, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water

For many long term therapies, there are existing products based on microsphere preparations which, while providing therapy for up to 3 months, experience a lag time of up to 2 weeks before drug release is sufficient to provide therapy. Over this time, where oral therapy is not a viable option, daily or more frequent injections of a short acting nature are required to provide the interim therapy. This example illustrates release of one such therapy, the antipsychotic drug risperidone (3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one), from a composition of the invention.

Data for the sustained release of risperidone from the lyotropic phase formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester are shown in Figure 11. Risperidone (20 mg) was dissolved in 1 g of 2,3-dihydroxypropionic acid octadec-9-enyl ester in a glass vial at 37°C, to this solution was added 70 µL pH4 acetate buffer (BP). The vial was rotated on a tube roller at 37°C for 1 hour. The entire sample of low viscosity precursor was injected into a 1 mL air-filled soft gel capsule and placed into a 50 mL polypropylene tube containing a 50 mLs of pH4 acetate buffer. This was sealed and placed on a shaking water bath at 80 rpm, 37°C. Samples were taken from the solution at regular

intervals, an identical volume of release medium replaced, and the samples were analysed for risperidone content by HPLC.

5 Example 15 – Sustained release of FITC-dextran from an injectable precursor composition of FITC-dextran, 2,3-Dihydroxypropionic acid octadec-9-enyl ester and Water

Many large hydrophilic molecules such as proteins used in therapy are difficult
10 to formulate in long acting depot injections. This example describes the sustained release of a representative large hydrophilic molecule, FITC-dextran (20,000 molecular weight), from injectable precursor based on 2,3-dihydroxypropionic acid octadec-9-enyl ester and the data is shown in Figure 12. FITC-dextran (20,000 molecular weight) (15mg) was dissolved in 102 µL of
15 pH7.4 phosphate buffer (BP). 70 µL of this solution was added to 930 mg 2,3-dihydroxypropionic acid octadec-9-enyl ester in a glass vial, which was rotated on a tube roller at 37°C for 1 hour. The entire sample of low viscosity precursor was injected into a 1 mL air-filled soft gel capsule and placed into 50mLs of pH4 acetate buffer in a 50 mL polypropylene tube. This was sealed and placed on a
20 shaking water bath at 80 rpm, 37°C. Samples were taken from the solution at regular intervals, an identical volume of release medium replaced, and the samples were analysed for octreotide content by size exclusion chromatography.

25 Example 16 - Production of an injectable, submicron dispersion containing 2,3-dihydroxypropionic acid octadec-9-enyl ester

Many drugs are poorly soluble in human blood, but can be administered as a solution in a dispersed lipidic medium such as an emulsion. For intravenous
30 therapy using such dispersed media, the particle size is favourable when below 1000 nm, to avoid embolism formation or vascular occlusion. This example describes the formation of a dispersion based on the surfactant 2,3-

dihydroxypropionic acid octadec-9-enyl ester, for which the particle size is less than 1000 nm.

5 Pluronic F127 (0.25g) was dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester (2.5g) at 70°C. This molten solution was injected via syringe into Water for Injections (22.25g) at 70°C over 5 seconds, while mixing at 11,000 rpm with an Ultraturrax homogeniser in a glass thermostatted vessel. This primary homogenisation was continued for 60 seconds after injection was complete. The resulting milky primary dispersion was transferred to an Avestin
10 C5 homogeniser thermostatted at 65°C, and subjected to 5 passes at 10,000 psi. The resulting fine dispersion was transferred to a glass beaker and with magnetic stirring was cooled slowly to 25°C. The particle size was investigated by Photon Correlation Spectroscopy on a Malvern Zetasizer approximately one hour after manufacture, and found to be 165.1 ± 0.6 nm with polydispersity index
15 of 0.053 ± 0.012 . After storage at 25°C for 21 days, the particle size was 302.4 ± 2.2 nm, with polydispersity index of 0.461 ± 0.020 .

Example 17 - Production of an injectable, submicron dispersion containing 2,3-dihydroxypropionic acid octadec-9-enyl ester and oleic acid

20

The solubility of basic drugs in lipids may be increased by addition of lipidic compounds containing acidic functional groups to form a lipophilic complex with higher molar solubility than the drug alone. This example illustrates that
25 addition of oleic acid to 2,3-dihydroxypropionic acid octadec-9-enyl ester does not alter the lyotropic phase formed by the lipid mixture, and can be used to produce a stable submicron dispersion.

Oleic acid was dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester at 6% w/w and, on contact with excess water, was observed to form reverse
30 hexagonal phase by crossed polarising microscopy, with the same texture as that formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester alone. Consequently a dispersion containing 2,3-dihydroxypropionic acid octadec-9-

enyl ester and oleic acid was produced as described. Pluronic F127 (0.25 g), and oleic acid (0.15 g) was dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester (2.35g) at 70°C. This molten solution was injected via syringe into Water for Injections (22.25g) at 70°C over 5 seconds, while mixing at 11,000 rpm with an Ultraturrax homogeniser in a glass thermostatted vessel. This primary homogenisation was continued for 60 seconds after injection was complete. The resulting milky primary dispersion was transferred to an Avestin C5 homogeniser thermostatted at 65°C, and subjected to 5 passes at 10,000 psi. The resulting fine dispersion was transferred to a glass beaker and with magnetic stirring was cooled slowly to 25°C. The particle size was investigated by Photon Correlation Spectroscopy on a Malvern Zetasizer approximately one hour after manufacture, and found to be 237.7 ± 2.7 nm with polydispersity index of 0.039 ± 0.024 . After storage at 25°C for 21 days, the particle size was 269.2 ± 1.4 nm, with polydispersity index of 0.158 ± 0.014 .

15

Example 18 - Production of an injectable, submicron dispersion containing 2,3-dihydroxypropionic acid octadec-9-enyl ester, oleic acid and irinotecan base

The inclusion of a basic drug (irinotecan, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1H-pyrano[3', 4': 6,7] indolizino[1,2-b]quinoline-3,14(4H, 12H) dione) into a dispersion formed by 2,3-dihydroxypropionic acid octadec-9-enyl ester and oleic acid as in Example 18, is described. Pluronic F127 (0.37 g), irinotecan base (0.25g) and oleic acid (0.30 g) was dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester (4.70 g) at 70°C. This molten solution was injected via syringe into 4.5% sorbitol solution in Water for Injections (44.38 g) at 70°C over 5 seconds, while mixing at 11,000 rpm with an Ultraturrax homogeniser in a glass thermostatted vessel. This primary homogenisation was continued for 60 seconds after injection was complete. The resulting milky primary dispersion was transferred to an Avestin C5 homogeniser thermostatted at 65°C, and subjected to 5 passes at 10,000 psi. The resulting fine dispersion was transferred to a glass beaker and with magnetic stirring was cooled slowly to 25°C. The particle size was investigated

by Photon Correlation Spectroscopy on a Malvern Zetasizer approximately one hour after manufacture, and found to be 188.6 ± 0.9 nm with polydispersity index of 0.044 ± 0.011 . After storage at 25°C for 28 days, the particle size was 257.2 ± 0.8 nm, with polydispersity index of 0.173 ± 0.012 .

5

Example 19 - Production of an injectable, submicron dispersion containing Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester

Pluronic F127 (0.12 g) was dissolved in 2,3-Dihydroxypropionic acid 3,7,11,15-tetramethyl-hexadecyl ester (1.25 g) at 80°C. This molten solution was injected via syringe into Water for Injections (23.63 g) at 80°C over 5 seconds, while mixing at 11,000 rpm with an Ultraturrax homogeniser in a glass thermostatted vessel. This primary homogenisation was continued for 60 seconds after injection was complete. The resulting milky primary dispersion was transferred to an Avestin C5 homogeniser thermostatted at 65°C, and subjected to 5 passes at 10,000 psi. The resulting fine dispersion was transferred to a glass beaker and with magnetic stirring was cooled slowly to 25°C. The particle size was investigated by Photon Correlation Spectroscopy on a Malvern Zetasizer approximately one hour after manufacture, and found to be 199.4 ± 1.0 nm with polydispersity index of 0.099 ± 0.008 .

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Example 20 - Production of an injectable, submicron dispersion containing 3,7,11-trimethyl-dodecyl urea

Pluronic F127 (0.12 g) was dissolved in 3,7,11-trimethyl-dodecyl urea (1.25 g) at 80°C. This molten solution was injected via syringe into Water for Injections (23.63 g) at 80°C over 5 seconds, while mixing at 11,000 rpm with an Ultraturrax homogeniser in a glass thermostatted vessel. This primary homogenisation was continued for 120 seconds after injection was complete. The resulting milky primary dispersion was transferred to an Avestin C5 homogeniser thermostatted at 65°C, and subjected to 5 passes at 10,000 psi. The resulting fine dispersion was transferred to a glass beaker and with

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magnetic stirring was cooled slowly to 25°C. The particle size was investigated by Photon Correlation Spectroscopy on a Malvern Zetasizer approximately one hour after manufacture, and found to be 429.6 ± 13.2 nm with polydispersity index of 0.384 ± 0.013 .

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Example 21 - Low haemolytic potential of injectable dispersion of 2,3-dihydroxypropionic acid octadec-9-enyl ester and oleic acid

10 In order to be useful for intravenous drug delivery an injectable dispersion should not cause substantial haemolysis of red blood cells on injection into the bloodstream. This example illustrates the low haemolytic potential of a composition of this invention.

15 Pluronic F127 (0.25g) was dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester (2.35g) and oleic acid (0.15g) at 70°C. This molten solution was injected via syringe into a 4.5 % sorbitol solution (22.25g) at 70°C over 5 seconds, while mixing at 11,000 rpm with an Ultraturrax homogeniser in a glass thermostatted vessel. This primary homogenisation was continued for 60 seconds after injection was complete. The resulting milky primary dispersion
20 was transferred to an Avestin C5 homogeniser thermostatted at 65°C, and subjected to 5 passes at 10,000 psi. The resulting fine dispersion was transferred to a glass beaker and with magnetic stirring was cooled slowly to 25°C.

25 This product was tested for in vitro haemolysis using a human erythrocytes suspension and measuring absorbance at 398 nm. It was tested against a control diluent which is accepted for intravenous injection, comprising propylene glycol 20%, Tween 80 4%, Benzyl alcohol 1.5 %, Maleic acid 1.6% and water to 100%. It was found that when incubated with human erythrocytes for 2 minutes
30 at 37°C, after centrifugation the absorbances were 0.33 and 1.80 for the product and control respectively.

Example 22 - Tolerability of injectable dispersion of 2,3-dihydroxypropionic acid octadec-9-enyl ester and oleic acid on Intravenous Administration

- 5 The acute tolerability is an important feature of an intravenously administered dispersion. Injectable products containing solvents are often not well tolerated in intravenous administration. This example illustrates that the intravenous administration of a composition of this invention is well tolerated.
- 10 Pluronic F127 (0.25g) was dissolved in 2,3-dihydroxypropionic acid octadec-9-enyl ester (2.35g) and oleic acid (0.15g) at 70°C. This molten solution was injected via syringe into a 4.5 % sorbitol solution (22.25g) at 70°C over 5 seconds, while mixing at 11,000 rpm with an Ultraturrax homogeniser in a glass thermostatted vessel. This primary homogenisation was continued for 60
- 15 seconds after injection was complete. The resulting milky primary dispersion was transferred to an Avestin C5 homogeniser thermostatted at 65°C, and subjected to 5 passes at 10,000 psi. The resulting fine dispersion was transferred to a glass beaker and with magnetic stirring was cooled slowly to 25°C.
- 20 The above product was diluted 50 % v/v with 5% dextrose solution and administered to rats. A total of four rats were dosed with this product by intravenous administration at 2 ml/kg of body weight at a rate of 0.1mL/minute into a jugular vein cannula. The rats were monitored for a total of 24 hours.
- 25 None of the rats exhibited any visible adverse reactions, which would be indicative of acute toxicity or non-tolerability.

Finally, there may be other variations and modifications made to the preparations and methods described herein that are also within the scope of the present invention.

5 DATED: 1 September 2003
PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
DBL AUSTRALIA PTY LTD

A handwritten signature in black ink, appearing to read "J. W. H. K.", is written below the printed text.

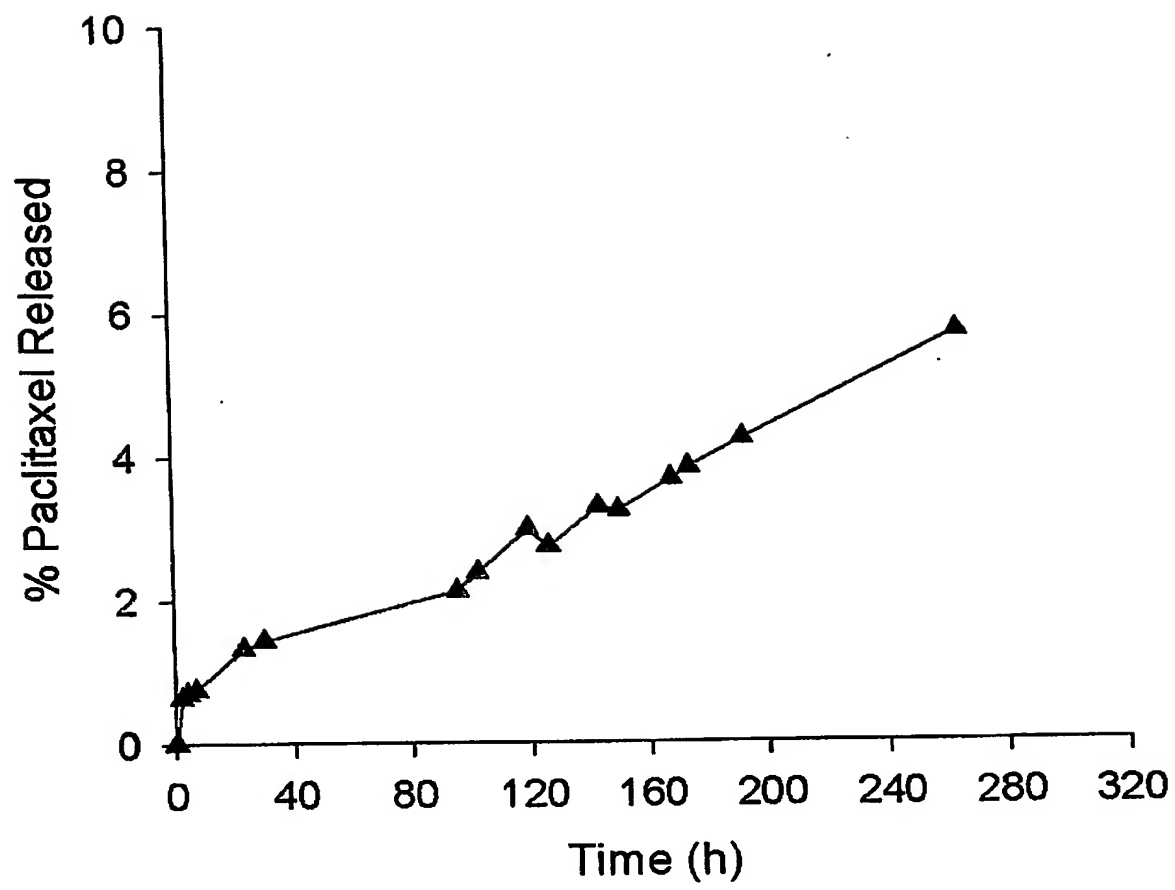


Figure 1

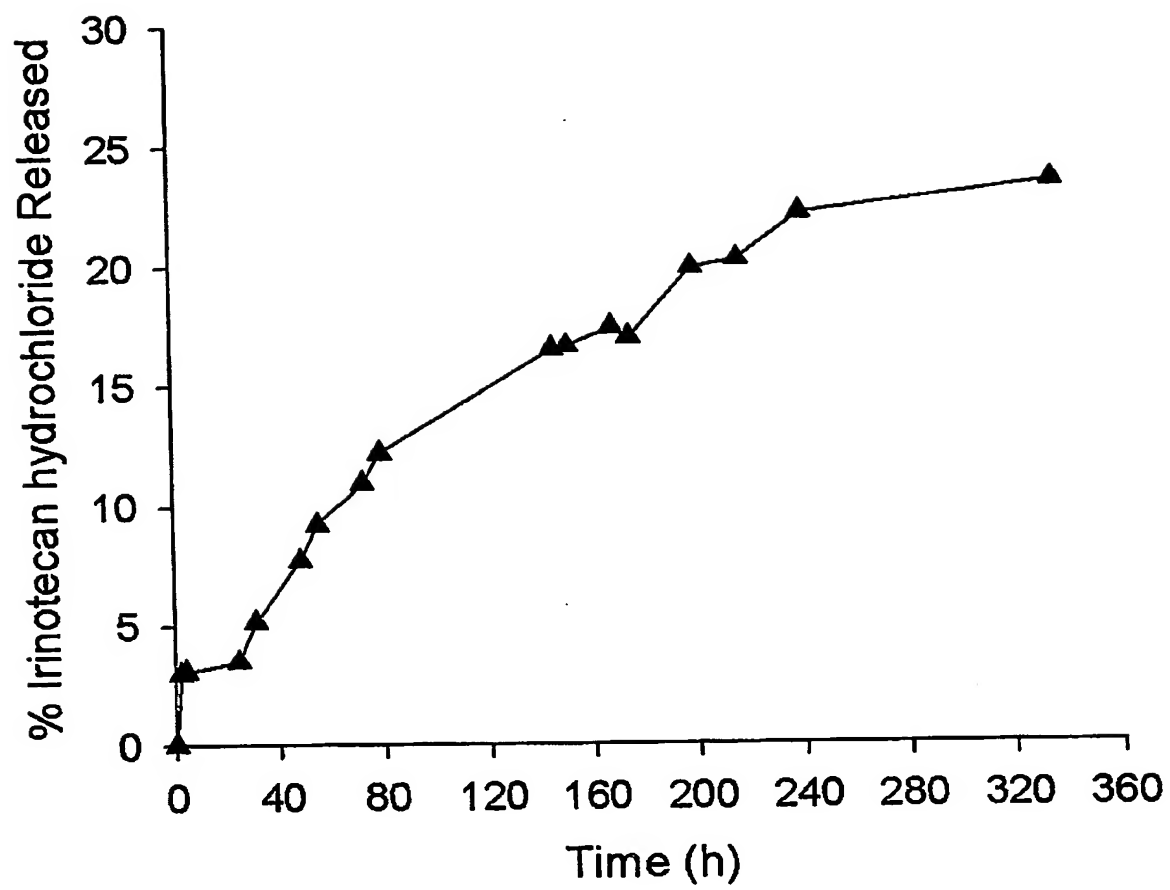


Figure 2

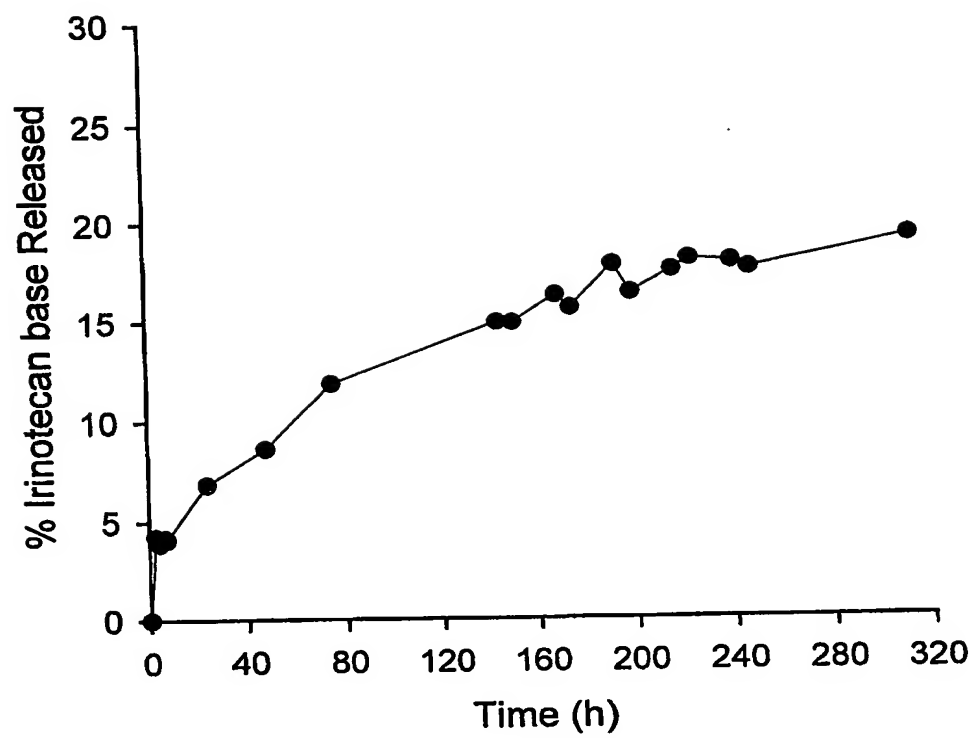


Figure 3

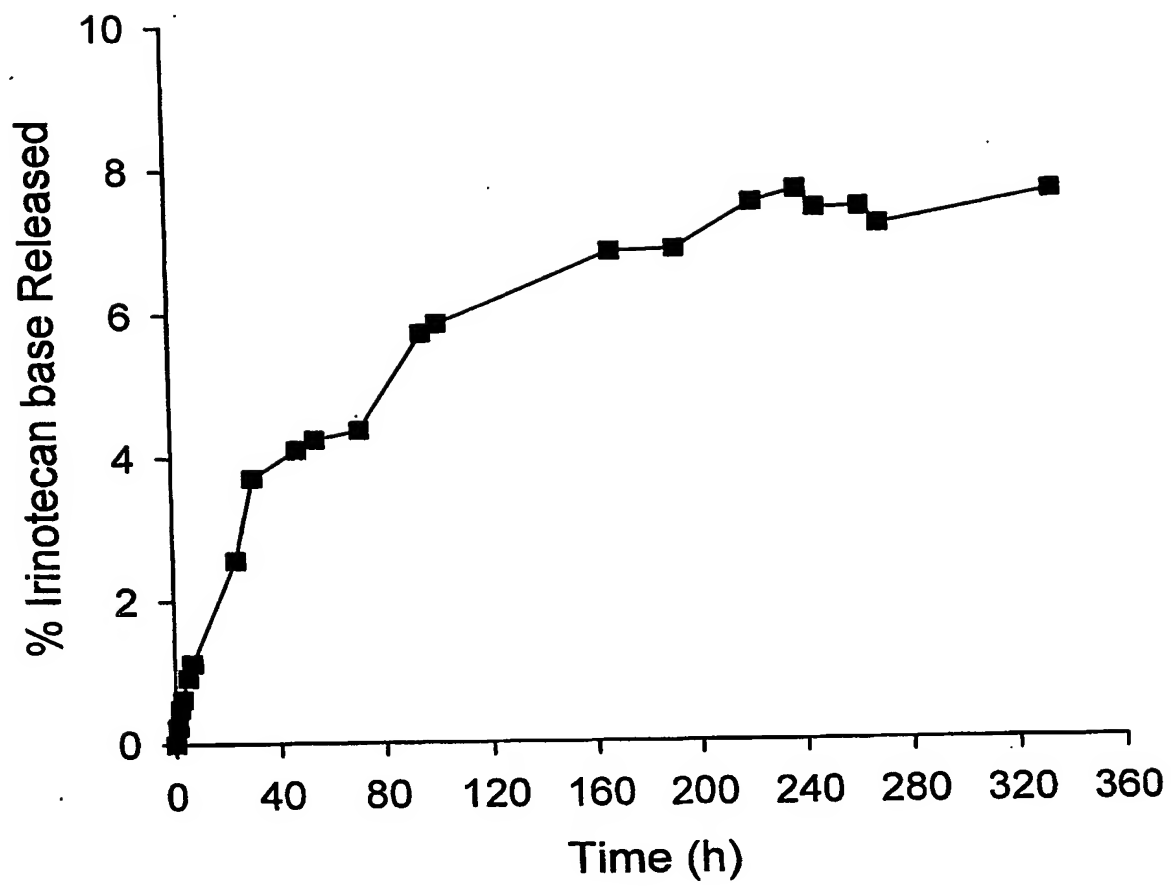


Figure 4

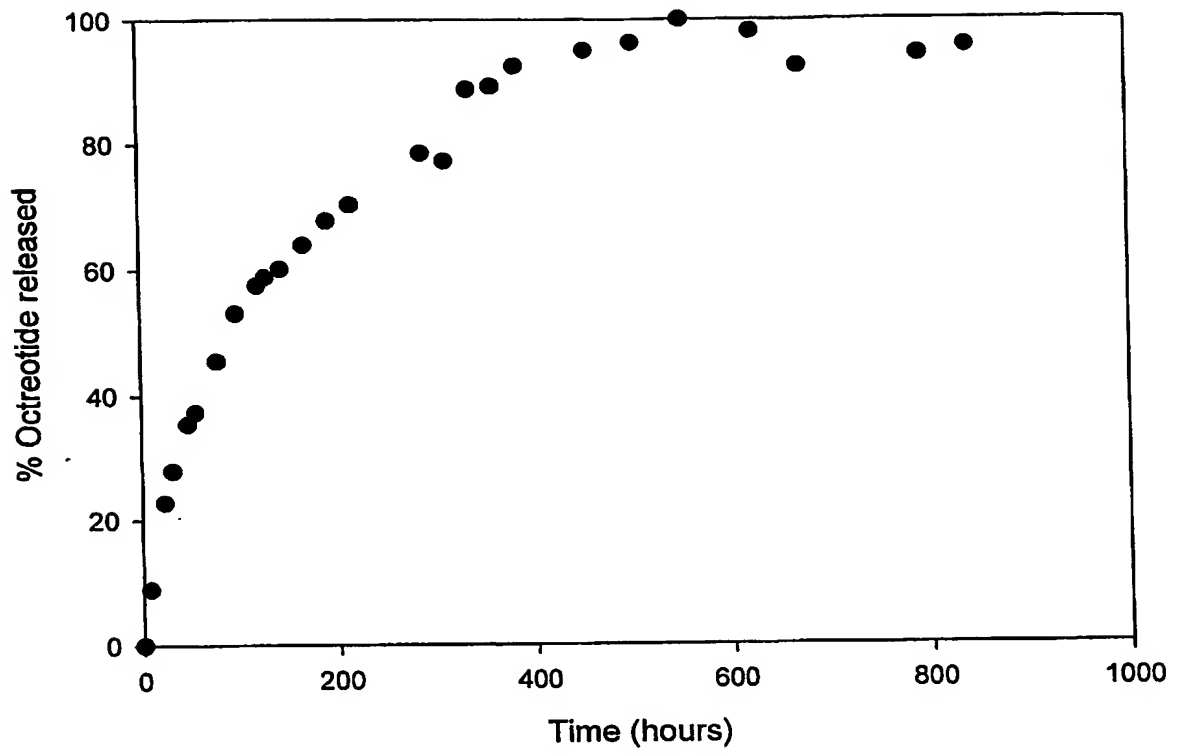


Figure 5

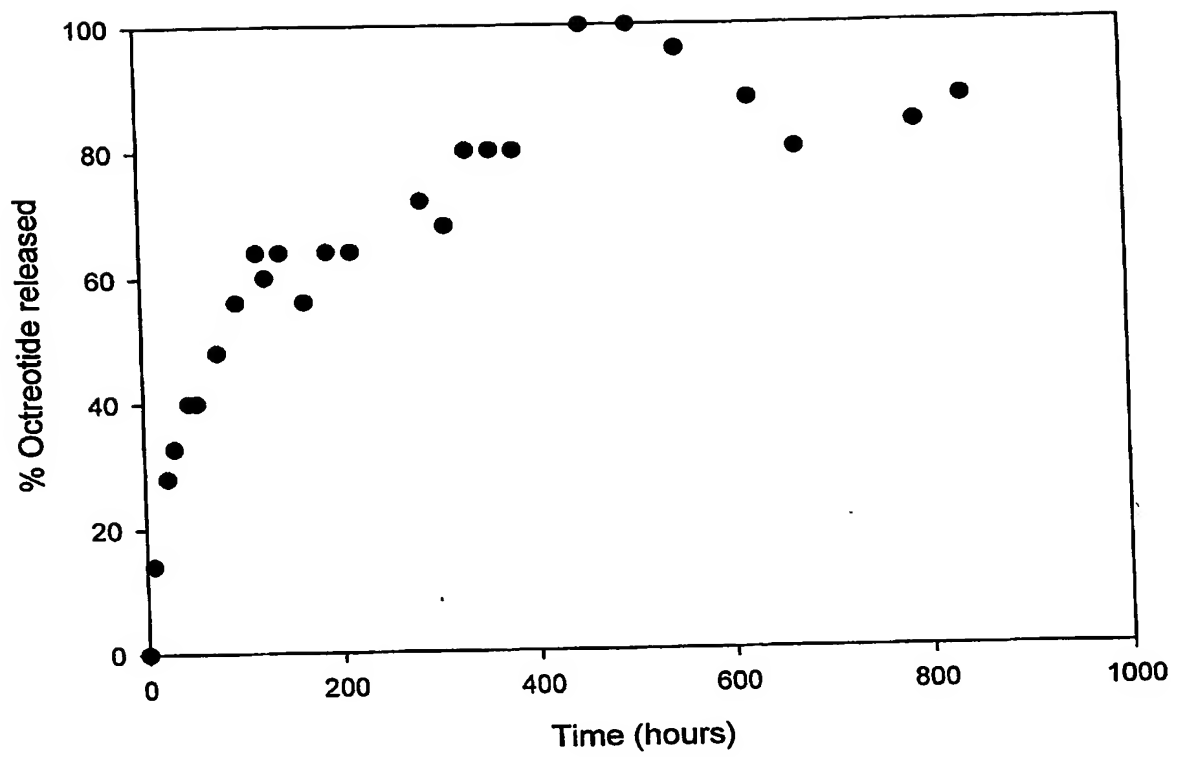


Figure 6

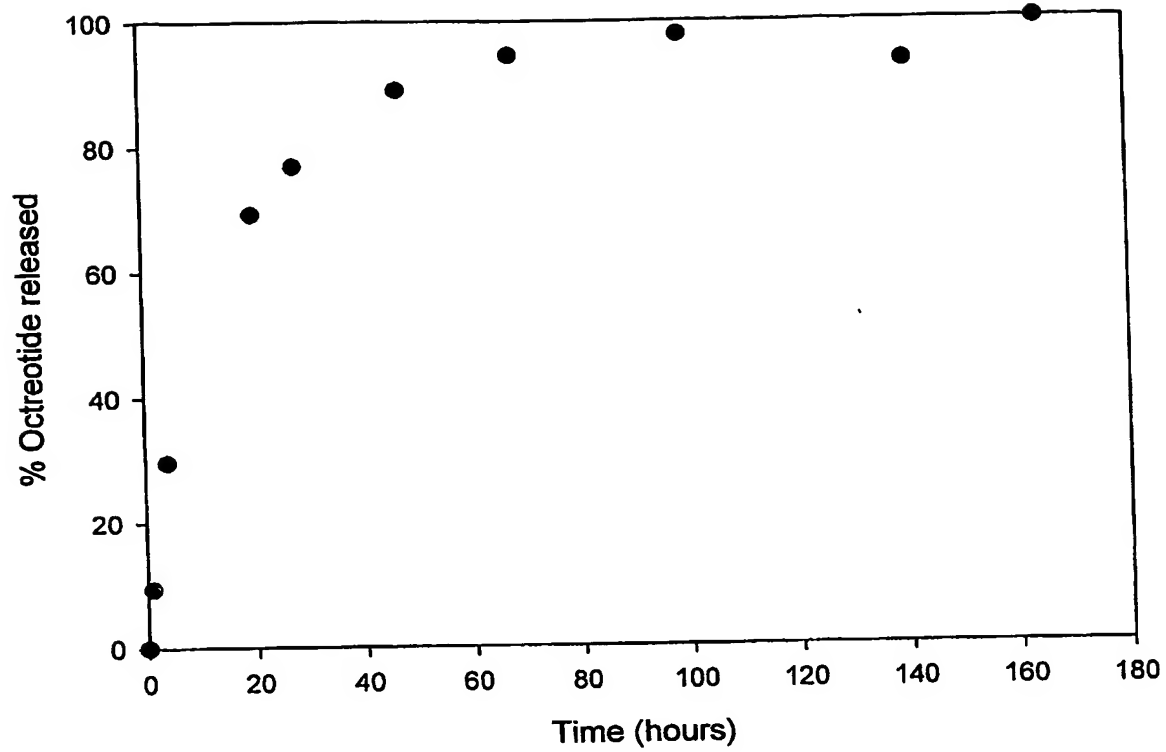


Figure 7

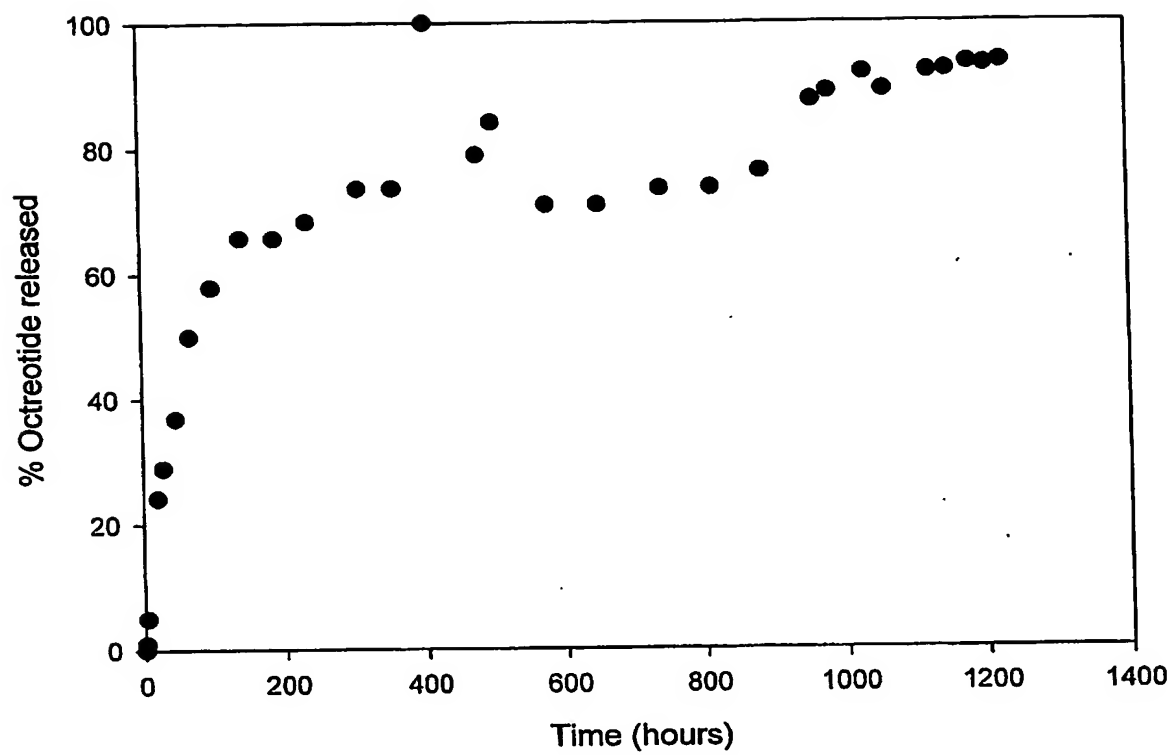


Figure 8

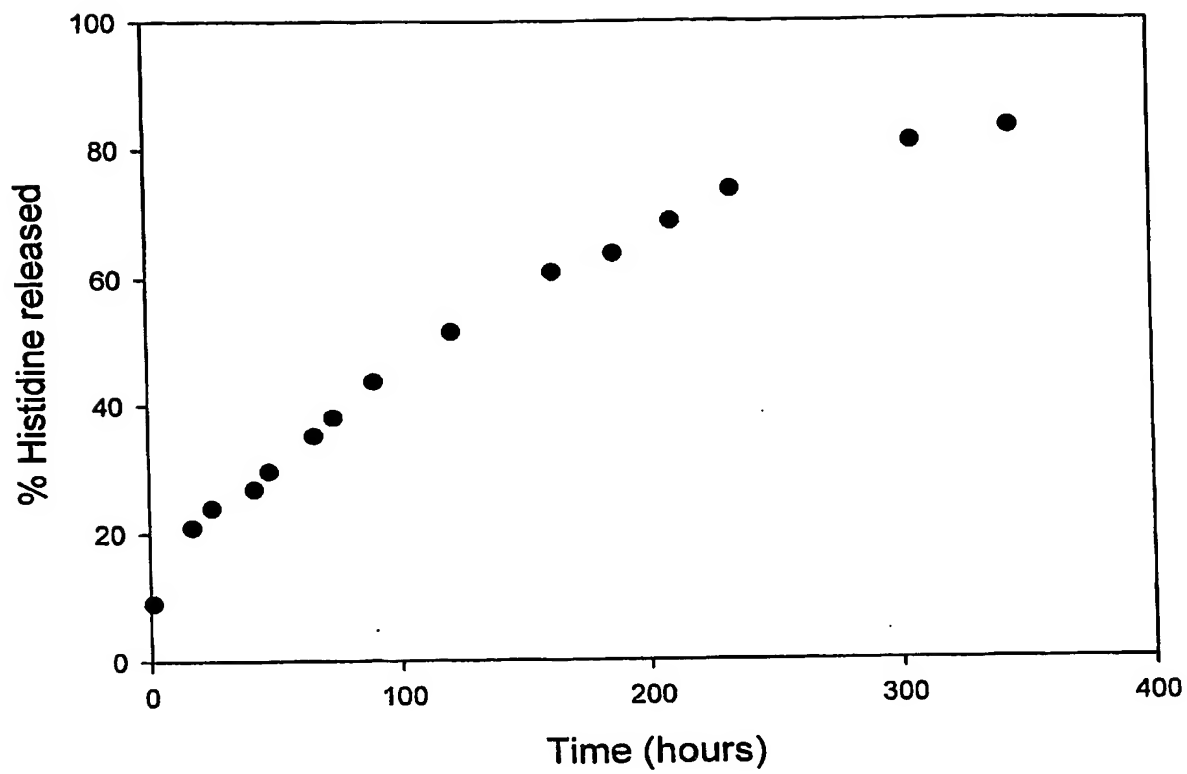


Figure 9

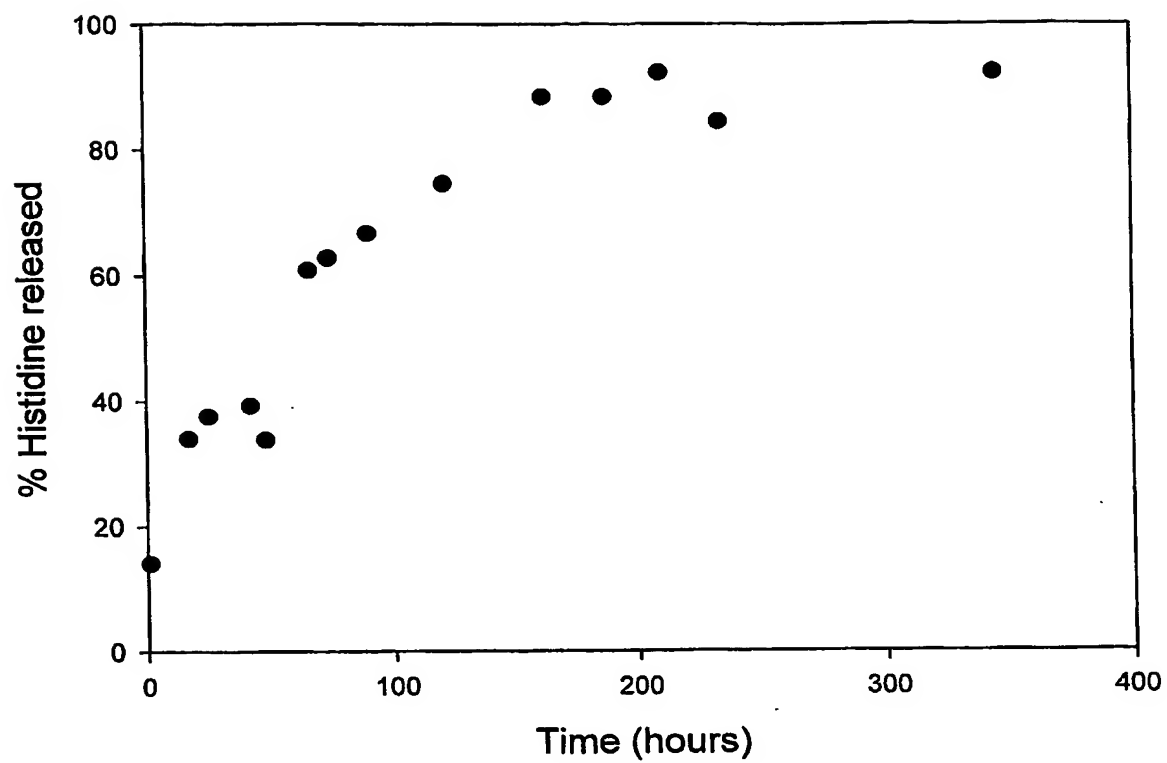


Figure 10

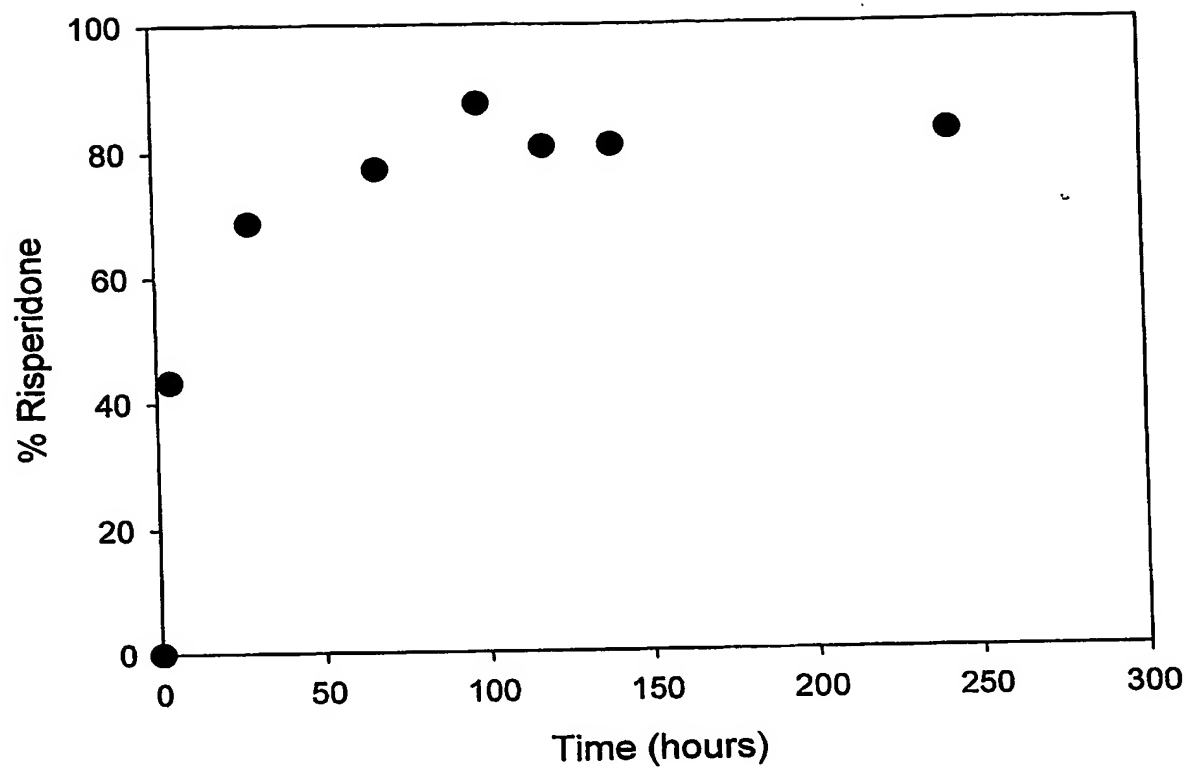


Figure 11

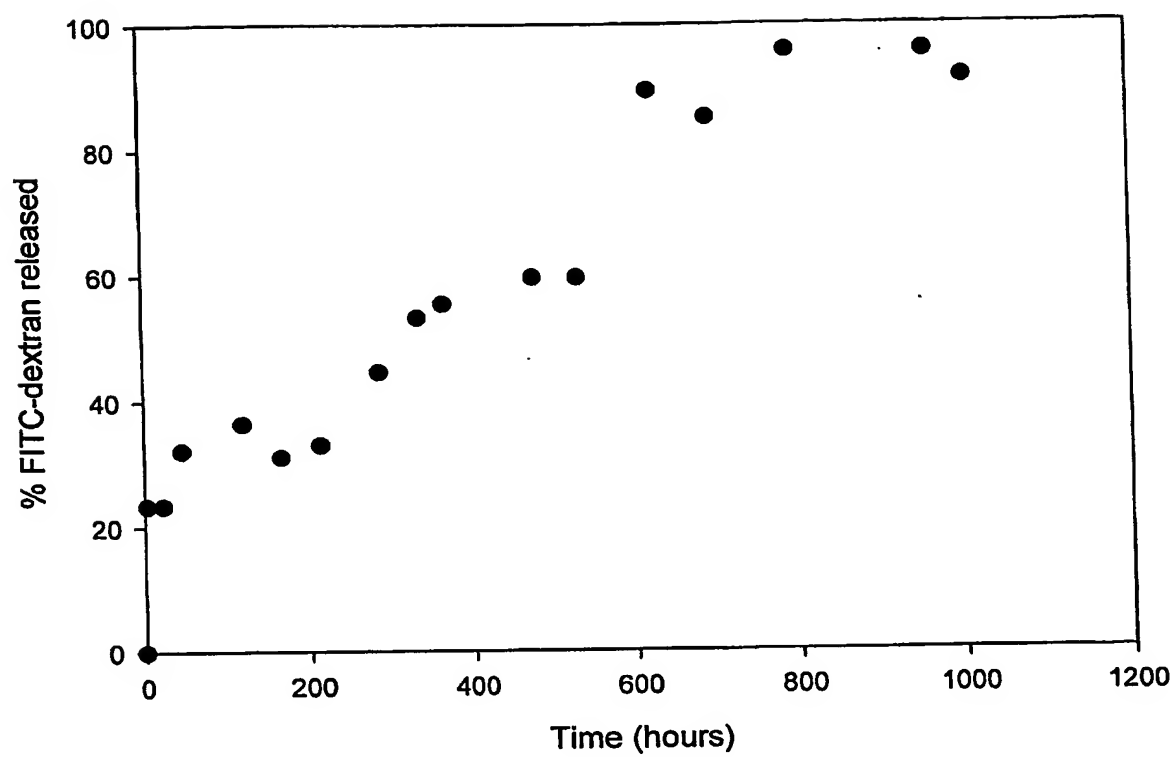


Figure 12